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REVIEW

Optimising Monoclonal Antibody Drug Development for Inflammatory Bowel Disease

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Abstract: Despite the success of monoclonal antibody (mAb) therapies in treating inflammatory bowel disease (IBD), a persistent therapeutic ceiling remains. This comprehensive review explores emerging strategies to enhance the efficacy of mAb-based treatments. Key among these is the development of bispecific antibodies designed to simultaneously engage two cytokine targets, offering dual blockade of inflammatory pathways and the potential for synergistic effects. Co-formulation approaches, comprising two or more mAbs within a single therapeutic product, are also examined as a means of broadening immunologic coverage and streamlining delivery. Finally, advances in pharmacokinetic optimisation are discussed, including Fc region modifications, polyethylene glycol conjugation, albumin fusion, and glycoengineering, all aimed at reducing immunogenicity and extending half-life. Together, these strategies represent a path toward next-generation biologics with the potential to minimise current limitations in IBD treatment.

Keywords: monoclonal antibodies, bispecific antibodies, drug development, immunogenicity, bioengineering, inflammatory bowel disease

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Introduction

The therapeutic armamentarium for the treatment of inflammatory bowel disease (IBD) has expanded rapidly in recent years, driven by a better understanding of the immunopathology that initiates and perpetuates intestinal inflammation. Monoclonal antibodies (mAbs) now target a range of immune mechanisms, including cytokines, integrins, and lymphocyte trafficking pathways.[1]

However, despite the development of new therapeutic agents there has not been a transformative shift in patient outcomes. Most advanced therapies induce clinical remission at 1 year in only 30–40% of patients at one year.[2] Furthermore, response rates decline with successive biologic exposure, likely due to immune adaptation.[3,4] This persistent therapeutic ceiling is a product of several limitations, including the narrow targeting of single immune pathways and pharmacokinetic (PK) challenges, such as immunogenicity.[5] While strategies like dose escalation and therapeutic drug monitoring have been explored they have yet to meaningfully overcome these barriers. The SONIC trial[6] showed that combination therapy with IFX and AZA was superior to monotherapy, while the VEGA trial[7] demonstrated that dual targeting with guselkumab (anti–IL-23) and golimumab (anti-TNFα) improved clinical responses in moderate-to-severe UC. Both support the potential of advanced combination therapy (ACT) using agents with distinct mechanisms of action. However, ACT has not been shown to sufficiently overcome the challenges posed by the therapeutic ceiling and there remains a pressing need to refine our use of mAbs to improve remission rates and long-term outcomes.

This narrative review examines how existing and novel therapeutic mAbs can be optimised to maximise clinical benefit for patients with IBD. To identify relevant articles, a PubMed search was conducted using the keywords "monoclonal antibody", "antibody engineering", "bispecific antibody", "antibody pharmacokinetics" and

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"immunogenicity". Filters for publication year and language were applied and reference lists of relevant articles were also screened to identify additional sources.

Improving Pharmacokinetics

Currently licensed mAbs for the treatment of IBD require relatively frequent administration, either intravenously in hospital infusion suites or via subcutaneous injection.[8] This presents several challenges which are frequently cited by patients as impacting upon quality of life,[9] including injection site reactions, adherence difficulties, and time away from work or caregiving responsibilities. It also places a burden on healthcare systems due to the significant costs associated with infusion facilities or contracts with homecare providers for subcutaneous delivery. Optimising the PK profiles of mAbs can help to, amongst other benefits, lengthen the dosing duration and address these issues (Table 1).

Modifying the Fc Region

One of the most effective ways to enhance mAb half-life is through modifications to the fragment crystallisable (Fc) region. The Fc region interacts with the neonatal Fc receptor (FcRn) which plays a key role in protecting IgG antibodies from lysosomal degradation.[10] By engineering the Fc region to increase its affinity for FcRn at acidic pH (but not at physiological pH), mAbs can be recycled – the mAbs undergo endocytosis and then migrate to the cellular membrane where they are released back into the circulation without undergoing catabolism – more efficiently, thereby prolonging their serum half-life.[10] This strategy has already been successfully performed in haematology with eculizumab, a mAb that was modified to have higher affinity for the FcRn to create ravulizumab,[11] a second generation mAb acting on anti-complement C5 used for paroxysmal nocturnal haemoglobinuria. These modifications allowed ravulizumab to be administered eight weekly instead of two weekly.[12]

Another strategy is to incorporate specific Fc mutations that are known to extend half-life of IgG antibodies into therapeutic mAbs. Examples of these are the YTE (M252Y/S254T/T256E), LS (M428L/N434S) and KF (H433K/N434F) mutations that result in a 10 to 12 fold increase in avidity for the FcRn in mice and non-human primates.[13] Data from two novel mAbs incorporating YTE modifications are shown in Figure 1 and demonstrate the improved serum half-life compared to comparative current therapies. However, these mutations can impact upon effector functions such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) which anti-TNFα mAbs are known to induce as part of their mechanism of action.[14] Modifications, such as using compounds other than sialic acid to modify the avidity for the

Table 1 Strategies Utilised to Optimise Pharmacokinetic Profiles and Reduce Immunogenicity in Monoclonal Antibodies

Strategy	Mechanism	Benefits	Examples	Limitations
Fc Region Engineering	Incorporate specific Fc mutations eg YTE, LS or KF	Reduce lysosomal degradation and increase half-life	Ravulizumab	Negative impact on effector functions
	Modification of glycans in the Fc region eg removal of fucose	Enhanced effector function	Obinutuzumab	Possible reduction in half-life
PEGylation	Conjugation with a polyethylene glycol molecule	Increased half-life, improved stability and reduced immunogenicity	Certolizumab	Steric hindrance can impair antigen binding and effector function
Albumin Fusion	Fusion of albumin or albumin-binding-domains to mAbs	Increased half-life	Ozoralizumab	Steric hindrance can impair antigen binding and effector function
Glycoengineering	Use of Glycodelete or Chinese hamster ovary cell lines can reduce immunogenic glycan incorporation	Enhanced effector function	Obinutuzumab	Challenges with industrial-scale implementation and potential impact on effector functions
Humanisation	Replacement of all the antibody, except the complementarity-determining regions, with human sequences	Reduced immunogenicity	Adalimumab	Ongoing structural changes can still lead to anti-drug antibody production
pI Modulation	Amino acid modification leads to changes in mAb isoelectric point	Improved distribution and clearanceγ	None currently	Increase risk of self-association and changes in viscosity

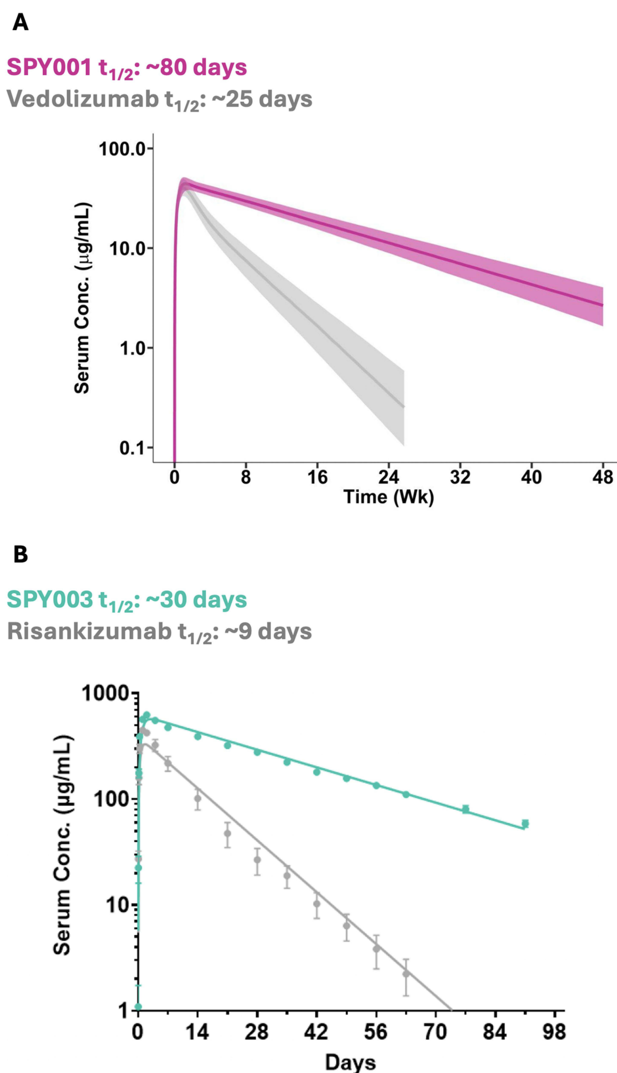

Figure 1 Examples of improved pharmacokinetic profiles of monoclonal antibodies with modifications to the Fc region. (**A**) SPY001 - a humanized monoclonal IgG1 antibody that binds to the same α4β7 epitope as vedolizumab and includes a YTE modification within the Fc region. Human data shows a significantly prolonged half-life compared to vedolizumab. SPY001 PK simulation based on PK data as of 03/19/2025 cutoff. Vedolizumab PopPK simulation based on published PK parameters of vedolizumab, Rosario, M, et. al. (2015). Data on file. Graph reproduced with permission from Spyre Therapeutics, Inc.[17–19] (**B**) SPY003 - a human monoclonal IgG1 antibody that binds to IL-23p19 and includes a YTE modification within the Fc region. Non-human primate data shows a significantly prolonged half-life compared to a synthesized comparator antibody with the same primary structure (i.e., sequence) as risankizumab. Graph reproduced with permission from Spyre Therapeutics, Inc.[20]
Abbreviations: Fc, Fragment crystallisable; IL-23, Interleukin-23; $t_{1/2}$, Half-Life; PK, Pharmacokinetic.

FcRn, have been shown to be effective at avoiding this impact on effector functions.[15] There is also evidence that excessively increasing binding affinity for the FcRn at neutral pH can actually hinder antibody release from the FcRn and paradoxically reduce circulation time.[16] Fc region engineering thus requires a delicate balance to optimize binding affinity and release dynamics and ensure there are no negative downstream effects on mAb efficacy.

Modifying the constituent sugar molecules of the Fc region, known as glycoengineering, is another potential technique to improve the PK properties and efficacy of mAbs. The Fc region in most IgG1-isotype mAb is bound to two complex oligosaccharides, such as fucose, and removal or blocking of this fucose has previously been shown to enhance ADCC activity.[21] This has been utilised to develop mAbs such as obinutuzumab, an afucosylated CD20-targeting antibody, that demonstrated superior activity over the CD20-targeting antibody rituximab and has received FDA-approval for treatment of patients with chronic lymphocytic leukaemia (CLL) and follicular lymphoma.[22,23] There are no current afucosylated mAbs licenced for IBD or immune mediated inflammatory disorders (IMIDs) but given the feasibility of the technology and the demonstrated impact upon NK cells via enhanced ADCC activity, it remains an area

of interest. Interestingly, data from rat models has suggested that glycoengineering may reduce the half-life of mAbs[24] and so further research on the impact on PK of this process is required.

Polyethylene Glycol Conjugation

Polyethylene glycol (PEG) conjugation, or PEGylation, is another strategy employed to improve mAb pharmacokinetics. PEGylation increases the hydrodynamic size of antibodies, which reduces renal clearance and proteolytic degradation and helps to improve solubility and stability allowing mAbs to be administered subcutaneously.[25,26] PEGylation may also play a role in immunogenicity, which is discussed in greater detail below.[27]

There are proven techniques, that allow a variety of different forms of PEG to be conjugated to either a mAb or antibody fragments, which have developed over the past four decades.[28] Certolizumab is an example of a PEGylated mAb licenced in IBD as well as other IMIDs, such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.[29] While PEGylation confers pharmacokinetic advantages, it can also interfere with antigen binding and effector function due to steric hindrance.[30] To address this, modern techniques such as selective acylation, reductive alkylation or the use of oxidising agents that allow site-selective PEGylation[31] away from the antigen-binding site can be used to preserve function whilst optimising PK profiles (Figure 2).

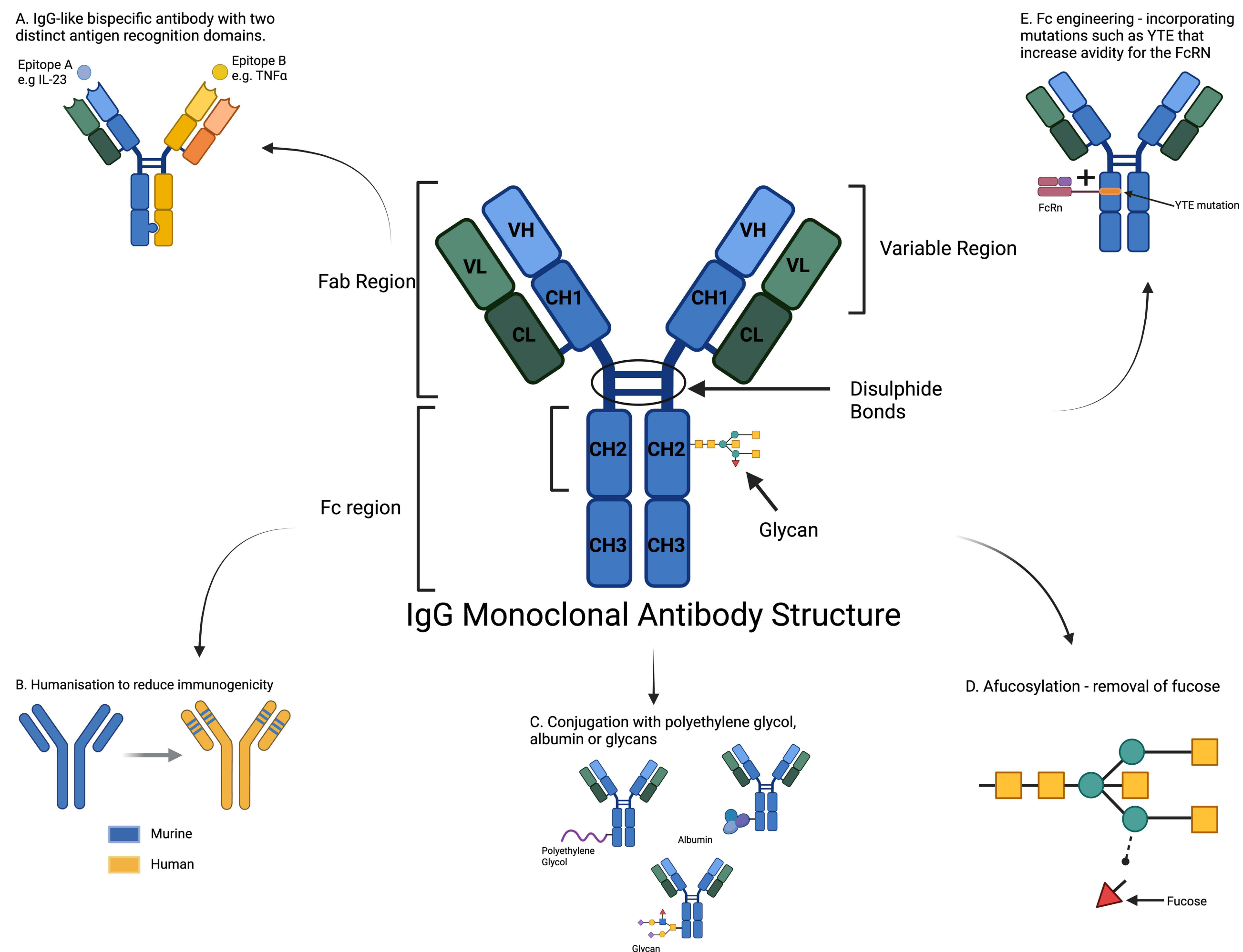

Figure 2 Examples of strategies to optimise monoclonal antibodies. (**A**) Bispecific antibodies. (**B**) Humanisation of antibodies to reduce immunogenicity. (**C**) Conjugation to improve pharmacokinetic profiles and reduce immunogenicity. (**D**) Afucosylation – removal of fucose to enhance effector function. (**E**) Fc region engineering such as incorporating mutations to improve pharmacokinetics. Created in BioRender. Colwill, M. (2025) https://BioRender.com/qcfqk5v.

Abbreviations: Fab, Fragment-antigen binding; Fc, Fragment Crystallisable; FcRn, Neonatal Fc Receptor; VL, Variable region of light chain; VH, Variable region of heavy chain; CH, Constant region of heavy chain; CL, Constant region of light chain; IL-23, Interleukin-23; TNFα, Tumour necrosis factor alpha.

Albumin Fusion

Fusing mAbs or antibody fragments to albumin or albumin-binding domains (ABDs) is an effective approach to prolong systemic exposure. Albumin, a naturally long-lived serum protein, benefits from FcRn-mediated recycling similar to IgG, with a half-life of approximately 19–21 days in humans.[32] Albumin fusion allows chimeric proteins to harness these PK advantages.[32] An early example is AlbudAb, which demonstrated albumin-like PK properties, including prolonged half-life and reduced renal clearance when assessed using radiolabelled zirconium-98 and serial PET imaging.[33]

This approach is particularly beneficial for antibody fragments, which are otherwise rapidly cleared via renal filtration. Although no albumin-fused mAb fragments are currently licensed for IBD, ozoralizumab is an anti-TNFα therapy that has been given regulatory approval in Japan for the treatment of rheumatoid arthritis.[34] It is a trivalent bispecific antibody (bsAb) fragment that, due to the presence of an anti-human serum albumin heavy chain antibody, has a prolonged half-life with clinical trial data demonstrating that it is effective at either four or eight weekly subcutaneous administration.[35,36]

However, fusion can also inadvertently impair antigen binding through steric hindrance which was seen with the Designed ankyrin repeat protein (DARPin) G3.[37] To mitigate this risk, advanced protein engineering techniques, such as flexible linker design or modification of the fusion position should be employed to preserve antigen recognition and maintain therapeutic efficacy.[38]

Engineering the Antibody Structure

Beyond modifications of the Fc region or conjugation, further engineering of the mAb structure offers opportunities to enhance PK profiles. This includes optimizing the variable region for improved stability, reducing immunogenicity, and modifying charge properties that influence tissue distribution and clearance.

The isoelectric point (pI) is the pH at which an antibody has no net electrical charge. Given that the surface membranes of most cells are negatively charged, antibodies need to be positively charged in order to undergo endocytosis.[39] Therefore, by manipulating the pI of mAbs, usually by lowering it, it is possible to alter both the rate of clearance and distribution of a drug.[40] However, this change in pI can also increase the risk of self-association and viscosity which can negatively impact upon their therapeutic efficacy.[41] Whilst previous studies have described the pI of multiple mAbs, including those used in IBD such as infliximab and adalimumab,[39] this technique has yet to be successfully applied in clinical practice.

Sortase-mediated ligation (SML) is another possible method of mAb structure modification that uses the enzyme sortase to attach various moieties to proteins at specific sites.[42] This allows the production of antibody-drug conjugates (ADC) in a manner that offers positive impacts on the PK of mAbs by providing precise control over the attachment site and also allows for modifications to the drug-antibody-ratio.[43] Recent advancements in overcoming problems with the SML process, such as stability and calcium dependence,[44] has led to suggestion that it offers great prospects for developing mAbs to in oncological, infections and autoimmune conditions.[42]

Furthermore, techniques such as the incorporation of unnatural amino acids to create ADCs have been shown to promote site specific delivery of mAbs in oncology with multiple therapeutic agents licenced[45] and can potentially positively impact PK profiles and efficacy.[46]

Reducing Immunogenicity

Immunogenicity remains one of the greatest challenges facing both current and emerging monoclonal antibody therapies. The host immune system can trigger the production of anti-drug antibodies (ADAs) which can result in reduced efficacy, altered PK profiles with increased clearance, and lead to hypersensitivity reactions.[47] To mitigate these issues, multiple strategies have been developed to reduce the immunogenic potential of therapeutic antibodies, focusing on molecular design and manufacturing control, in the hope of improving or prolonging the effect of mAbs (Table 1).

Humanization of Antibodies

One of the earliest strategies developed to reduce immunogenicity is antibody humanization. Initial therapeutic mAbs were derived from murine sources and contained murine proteins which were recognized as foreign by the host immune

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system leading to the development of ADAs that neutralized their therapeutic effect.[48] Chimeric antibodies, which combine murine variable domains with human constant regions, were developed however these still contained 30–40% non-human sequence and therefore still elicited significant immune responses.[49]

To address this, the process of humanisation was developed which involves retaining only the complementarity-determining regions (CDRs) – ie short segments within the variable portions of the mAb that bind to the antigen – and replacing the rest of the antibody structure with human sequences reducing the non-human content of mAbs to under 10%.[50] This is achieved through genetic engineering using a hybridoma of murine B cells, which allows for a stable source of mAbs, and involves isolating and cloning the mouse DNA encoding the mAb. The DNA for the constant region of the mouse antibody is then replaced with human DNA sequence whilst the CDR is left intact throughout this process. The human/murine hybrid gene is then inserted into a second hybridoma for production of the humanised mAb.[51,52] An example relevant to IBD is adalimumab, a fully human anti-TNFα mAb, which demonstrated a low ADA incidence compared to some other mAbs, such as infliximab.[53] However, ADA production and immunogenic loss of response is still seen, possibly due to the mAb undergoing structural changes or containing novel epitopes introduced during engineering.[54] Therefore whilst humanisation significantly reduces the immunogenic potential, it does not eradicate it completely and treatment with mAbs will still result in ADA production to varying degrees (see Table 1 in Harris & Cohen 2024, *BioDrugs*).[55] Given this, other strategies are required to reduce immunogenicity and further examples are discussed below.

Post Translation Modification

Glycoengineering, a post-translational modification technique involving the attachment of sugar moieties to proteins including therapeutic mAbs, was discussed earlier with regards to improving the PK profile of mAbs but it also has a role in reducing immunogenicity.

In order to initiate effector functions, IgG molecules – the structural class that makes up the majority of mAbs – are *N*-glycosylated at the conserved asparagine position, Asn297, in the Fc region.[56] Due to the use of murine cell lines for expression, non-human glycan structures, such as galactose-α-1,3-galactose, can be inadvertently incorporated into mAbs and this can lead to the generation of ADAs and hypersensitivity reactions against unexpected targets.[57] A cautionary example is cetuximab, a chimeric mouse-human IgG1 mAb against epidermal growth factor, which was found to have caused anaphylaxis due to the production of IgE to galactose-α-1,3-galactose.[58]

To reduce this risk and the immunogenicity of mAbs, newer techniques using human or similar cell lines, such Chinese hamster ovary cells (CHO) where glycosylation patterns are very similar to humans, have been developed to avoid immunogenic glycan incorporation.[59] Additionally glycoengineering technologies like GlycoDelete also allow for precise control of glycan structures which can help to minimise immunogenic potential whilst enhancing PK profiles and potentially therapeutic efficacy.[60,61]

PEGylation, described earlier, had been suggested to reduce immunogenicity of proteins as early as the 1970s.[62,63] While there may be PK benefits, the impact of PEGylation on the immunogenicity of mAbs is less clear and work using mouse models has found that compounds that undergo the same PEGylation process can produce varying levels of immunogenicity.[27] Therefore, whilst it is a well-understood and commonly used technique, the impact of PEGylation on reducing immunogenicity of novel mAbs must be assessed on an individual basis.

Fc Engineering and Aggregation Prevention

The Fc region of mAb, while critical for immune effector function, also presents a site of potential immunogenicity if not carefully managed. Fc engineering can reduce this risk by minimizing unwanted immune activation or aggregation.[55]

Mutations or modifications to the Fc region – such as the IgG1 variant L234A/L235A (LALA) – can prevent interaction with Fcγ receptors (FcγR) and complement proteins, thereby reducing immunogenicity.[64] These Fc mutations can also silence effector function and are therefore especially useful in therapeutic contexts where this is desirable, such as blocking cytokines or receptors. All three of vedolizumab, mirikizumab and risankizumab are licenced for IBD and contain such Fc modifications and demonstrate the plausibility of this technology for real-world practice.[65] There are

several other types of mutations or modifications, such as the STR mutation in the CH2 domain of the Fc, that offer promise in Fc engineering of mAbs to reduce immunogenic potential.[65]

Another major source of the immunogenicity of mAbs is protein aggregation. Aggregation has been shown to augment antigen-presentation and enhance phagocytosis and subsequent serum clearance of mAbs either by enhancing binding to FcγRs or through activation of complement pathways via Fc regions.[66] Aggregated mAbs also undergo structural changes that may lead to immune responses that target novel and unintended epitopes, resulting from either chemical modification or epitopes that were unavailable prior to aggregation because they were hidden by a native fold, exacerbating immunogenicity and clearance.[67]

Conformation and colloidal stability have been shown to be crucial factors in preventing aggregation.[68,69] Achieving greater stability can be done through changes during the manufacturing and formulation process, for example avoiding thermal stress by modifying the process of fast-freezing, required during lyophilisation, thereby reducing aggregation from cold denaturation.[70] Two techniques discussed earlier, PEGylation and glycosylation, have also been shown to reduce aggregation. PEGylation appears to protect against aggregation from thermal stress or pH[71] and glycosylation has been shown to protect against heat induced aggregation in the example of the protein alpha-chymotripsin.[72] However, both these techniques currently face challenges with large scale manufacturing and their real-world benefit with regards to preventing aggregation of mAbs is currently unclear.[66] An alternative approach, which has already been demonstrated to be successful and feasible on a large scale, is in the example of adalimumab where modifications were made by adding glycosylation sites into the Fab regions rather than modification of existing glycosylation sites or PEGylation. This process enhanced the melting temperature of the Fab and reduced aggregation and subsequent immunogenicity.[73]

Optimizing the Manufacturing Process

Beyond changes to the molecular structure, manufacturing quality plays a crucial role in the immunogenicity of mAbs because even fully human, well-engineered antibodies can elicit immune responses if manufacturing introduces impurities, contaminants, or structural variants.[74] Variability in a variety of factors can result in altered immunogenicity and ensuring process consistency along with rigorous control of both upstream and downstream processing steps is essential.

Host cell proteins (HCP), essentially impurities that originate from the host cells used during manufacturing, can often co-purify with mAb at trace amounts.[75] HCPs can contribute to immunogenicity, either directly or as adjuvants, and this can impact upon the efficacy of mAbs.[55] An example is phospholipase B-like 2 (PLBL2) which was found to be an HCP impurity in a preparation of lebrikizumab, use to treat asthma, and derived from CHO cells. More than 90% developed of participants developed an immune response to PLBL2 in trials impacting upon the efficacy of the drug.[76] Several techniques are available to remove HCPs[77] such as caprylic acid precipitation which has been shown to be effective at removing HCP impurities without impacting the efficacy of mAbs.[78] More recently, the use of activated carbon membranes, essentially working as an advanced filtration system, has been shown to be effective at removing these impurities whilst also improving the economy and efficiency of HCP removal.[79]

Chemical degradations that can occur during manufacture can introduce further impurities. Processes such as oxidation, deamidation, and isomerization, are all known to increase immune activation potential toward mAbs.[80] Thus, quality control measures should include an analysis of the propensity to undergo chemical alteration events and ideally offer real-time identification of these alterations so that filtration and purification techniques can be applied to ensure homogeneous production of mAbs with minimal immunogenic potential.

The presence of T and B cell epitopes can also contribute to the immunogenicity of mAbs and novel epitopes can inadvertently arise during manufacture.[55,81] Linear epitopes, fragments of the amino acid sequence of a mAb, can be recognized by both T and B cells whereas conformational epitopes, formed by amino-acids that are close in three dimensional structure but not necessarily contiguous in the primary sequence, can only be recognised by B cells.[82] These epitopes can be presented by class II human leucocyte antigens, recognised and then bound by T or B cell receptors to initiate CD4+ cells resulting in ADA production.[82] Reducing the formation of these epitopes during manufacture remains a challenge but there is evidence that the use of artificial-intelligence (AI) methods may be able to aid in the design of mAbs with reduced epitope formation.[83] AI can also be used to improve analysis of novel mAbs

and predict potential epitopes that may form via tools such as the Immune epitope database analysis resource (IEDB-AR).[84]

Other advanced bioprocessing technologies can assist with reducing immunogenicity by enhancing the manufacturing process. Machine learning algorithms such as NetMHCIIpan 4.0, which is able to predict peptide-HLA binding affinities, can assist in the identification of immunogenic hotspots within mAb sequences.[85] These models can be combined with mass spectrometry analysis in automated workflows to monitor production and identify critical parameters in real-time that impact upon immunogenicity.[86]

Dual Cytokine Targeting: Synergistic Modulation

The immunopathogenesis of IBD involves a complex interplay between innate and adaptive immune responses, microbial dysbiosis, epithelial barrier dysfunction, and genetic predisposition.[87] Cytokines such as TNFα, interleukin (IL)-12, IL-23, IL-6, IL-17, TNF-like ligand 1A (TL1A), and interferons are dynamically regulated during disease progression and in response to therapy.[88] Cytokine networks exhibit considerable redundancy and compensation, such that inhibiting one pathway may lead to upregulation of others.[89] This functional overlap is thought to contribute to the therapeutic ceiling observed with current biologic treatments, as targeting individual cytokines often fails to overcome this complexity.[88] Therefore, therapeutic approaches that simultaneously target multiple components of the inflammatory cascade are more likely to overcome this barrier and achieve improved clinical outcomes.

Combination therapy has previously been shown to be efficacious. The SONIC trial demonstrated enhanced clinical outcomes by combining an immunomodulator with an anti-TNFα agent[6] and more recently both the VEGA[7] and EXPLORER[90] trials have supported the greater efficacy of ACT. However, the use of multiple agents raises concerns regarding safety, tolerability, and cost,[91] challenges that could potentially be addressed by a single agent capable of simultaneously targeting multiple inflammatory pathways.

Bispecific Antibodies

BsAbs are engineered molecules that are designed to recognise two distinct epitopes or antigens.[92] Although they have been a subject of research interest for over 30 years, first-generation bsAbs failed to provide a significant clinical impact. Their development has been hampered by unique design challenges due to the complexity of assembling two different antigen-binding sites into one molecule and the resulting structural asymmetry that can interfere with function.[93] However, advances in recombinant DNA technology have led to significant improvements in bsAb design. Techniques such as the "knobs-into-holes" mutations, common light chain usage, and controlled fragment antigen binding (Fab)-arm exchange have significantly improved the structural integrity and functionality of bsAbs.[94] This has reinvigorated interest in bsAbs as therapeutic agents.

BsAbs can be broadly broken down into three structural classes:[95] antibody fragments or scaffold proteins fused to an antibody Fc region or human albumin solution, antibody fragments which lack an Fc domain, or fully IgG-like bsAbs. Each class offers distinct advantages and limitations, for example, IgG-like bsAbs generally exhibit prolonged half-life, while smaller formats such as bispecific T-cell engagers (BiTEs) provide enhanced tissue penetration.[96] One of the earliest clinically approved examples is blinatumomab, a BiTE antibody used for the treatment of acute lymphoblastic leukaemia.[97] It is produced using recombinant DNA technology in *Escherichia Coli* (E. coli) expression systems and composed of two single-chain variable fragments (scFvs) connected by a flexible linker and is expressed in the form of inclusion bodies within bacterial cells. These inclusion bodies are isolated, solubilized, and then subjected to refolding processes under controlled redox conditions to ensure correct disulfide bond formation and proper folding. Following refolding, the protein undergoes purification using chromatographic techniques such as size-exclusion chromatography.[98] While blinatumomab demonstrates superior tumour penetration, its bacterial origin necessitates rigorous quality control to ensure structural integrity, functional stability, and minimal endotoxin levels to avoid a theoretical infectious risk to patients.[99]

BsAbs can be further modified during manufacture to optimise pharmacological properties and improve efficacy. Key areas of focus include improving expression yield, stability, and manufacturability, while addressing issues like chain mispairing and aggregation which have historically hampered clinical efficacy.[100]

Several bsAbs targeting various cytokines are currently in development (Table 2). Dual targeting of TNFα and IL-23 is a logical strategy as it has previously been demonstrated that in patients who do not respond to anti-TNFα therapy, intestinal TNF-R2+IL-23R+CD4$^+$ T cells continue to be activated by IL-23 secreted from CD14+ macrophages – despite inhibition of TNFα – and they continue to promote pro-inflammatory effects via the IL-23R/Signal transducer and activation of transcription (STAT) 3 pathway.[101] Consequently, co-inhibition of IL-23 and TNFα is hypothesised to yield superior therapeutic outcomes. Two novel bsAbs targeting TNFα and IL-23 are currently in development, with Phase 2 trials anticipated.[102,103]

Dual-targeting TL1A and IL-23 is another combination of interest. TL1A and its functional receptor DR3 play key roles in IBD and other IMIDs and several TL1A inhibitors are being investigated in clinical trials with promising early data.[104,105] In vitro and in vivo studies have shown that TL1A enhances both innate and adaptive immune responses through actions on T cells, NK cells and innate lymphoid cells.[105,106] In IBD, TL1A and IL-23 are over-expressed in inflamed colonic mucosa compared to healthy controls[107] and in vitro studies have also shown that TL1A and IL-23 act synergistically to amplify mucosal inflammation through several mechanisms including induction of Th1 and Th17 immune responses.[108] A bsAb targeting IL-23 and TL1A has been developed and early data from in vitro and in vivo studies have demonstrated a synergistic therapeutic effect of co-targeting these two cytokines.[109]

Further bsAbs targeting TL1A are in the pipeline. HXN1002 targets both TL1A and α4β7 integrin, which mediates the homing of lymphocytes to gut-associated lymphoid tissue via binding to MAdCAM-1 on endothelial cells.[110] Preclinical studies presented by SPYRE Therapeutics in 2025 showed enhanced efficacy of dual inhibition in murine

Table 2 Bispecific Monoclonal Antibodies Currently Under Development for Use in IBD and IMIDs

Molecule	Targets	Indication	Trial Phase	Key Findings
V56B2	TNFα/IL-23p19	IBD	Pre-clinical	Ex vivo colonic biopsies from UC mice model showed reduction in phosphorylation of signal proteins associated with IBD and inflammation.
SOR102	TNFα/IL-23p19	IBD	Phase 1b	Greater improvements in Mayo score and modified Mayo score clinical response in BD vs OD daily dosing regime. Overall safe and well tolerated.
HXN1002	α4β7/TL1A	IBD	Pre-clinical	Comparable binding activity compared to parent mAbs. Enhanced α4β7 internalization and degradation compared to parent mAbs in in vitro and in vivo animal models.
PT-101	IL-6/IL-17A	UC	Phase 1b	Completed, results pending.
HXN1003	TL1A/IL-23-19	IBD / Dermatitis / Psoriasis	Pre-clinical	Comparable binding activity compared to parent mAbs. Synergistic therapeutic effects in in vitro and in vivo animal models.
PRV-3279	CD32B/CD79	Systemic Lupus Erythematosus	Phase 1 (Phase 2 ongoing)	The bsAb inhibited B cell function without depletion in healthy volunteers. No concerning safety signals.
ABT-981 (Lutikizumab)	IL-1α/IL-1β	Hidradenitis Suppurativa	Phase 2 (Phase 3 ongoing)	300mg every other week showed higher response rates (p=0.027) compared to placebo. No significant different in treatment-emergent adverse events compared to placebo.
XmAb5871 Obexelimab	CD19/FcγRIIb	IgG4 Disease	Phase 2 (Phase 3 ongoing)	80% (12/15) achieved primary endpoint of decrease of 2 or more from baseline in IgG4-related disease responder index. No concerning safety signals.

colitis models, and a Phase 2 study evaluating the extended half-life antibodies as single agents and pairwise combinations that started in 2025.[111]

Other cytokine pairs of interest include IL-6 and IL-17A, both of which contribute to inflammation in several IMIDs and appear to act synergistically in a positive feedback loop.[112] Preclinical data suggest that dual-inhibition of these two cytokines with the bsAb PT-101 could yield enhanced efficacy compared to each cytokine alone and phase 1b trials have been completed in patients with UC with the results awaited.[113] Other novel bsAbs, such as FL-BsAb1/17 which inhibits both IL-1β and IL-17A[114] or ABT-122, which inhibits both IL-17 and TNFα,[115] have previously shown promise in animal models, though neither remains in active development.

The novel agents described currently lack long term safety data and there are possible concerns with regards to infection, liver injury and malignancy.[91,116,117] Data from oncology has also demonstrated that the dual targeting mechanism of bsAbs can cause cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in 1–8% of patients.[118] CRS can present with fever, hypotension and multi-organ failure and be challenging to distinguish from sepsis[119] whilst ICANS can cause headaches, confusion, seizures and coma.[120] Large scale clinical trials and long term data will be required to understand the risks of bsAbs in patients with IBD.

Beyond mAbs, dual inhibition of Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) has also emerged as a promising strategy.[121] This approach may offer synergistic therapeutic effects while reducing side effects due to the more restricted cytokine profile mediated by TYK2.[122] A phase 2b study of brepocitinib, a dual JAK1/TYK2 inhibitor, in ulcerative colitis was reported in 2023 with positive results compared to placebo for inducing remission without any short term safety concerns.[123] Further trial data are awaited.

Co-Formulation

In addition to careful target selection and bsAb optimisation, co-formulation represents an emerging strategy of interest. Although often used interchangeably with co-administration, co-formulation specifically refers to the delivery of a single formulation containing two or more distinct therapeutic agents.[124] Key advantages of co-formulations include synergistic efficacy by co-targeting distinct inflammatory pathways, eg TNFα and IL-23, in a fixed ratio for example a 1:1 or 3:1 molar ratio of anti-TNFα to anti-IL-23 mAbs.[125] The optimum ratios for differing combinations remain undefined; however, this also presents an opportunity for more personalised treatments by tailoring co-formulation ratios based on individual patient biomarkers, disease phenotype and drug history. Moreover, co-formulation can also improve patient compliance by reducing pill or infusion burden, a factor known to improve treatment durability and clinical efficacy.[126]

The co-formulation of mAbs also presents significant formulation and analytical challenges due to the complex interactions between multiple protein therapeutics in a single solution. Unlike single-agent products, co-formulated biologics must accommodate different stability profiles, which can lead to non-native interactions and heterogeneous aggregation.[127] Proteins often require specific pH levels, excipients, and ionic strengths to remain stable, but combining them necessitates compromised formulations that may destabilize individual components.[128]

Most mAbs used in IBD are currently administered subcutaneously, adding an additional layer of complexity. Co-formulated products may require high protein concentrations, up to 300 mg/mL, leading to increased viscosity, colloidal instability, and a greater risk of aggregation, all of which can limit their suitability for subcutaneous delivery.[129] Furthermore, if fixed but varying ratios of mAbs are needed within a single product, this introduces additional manufacturing complexity and quality control demands.

External factors such as freeze-drying, agitation, and temperature fluctuations can adversely impact product quality, necessitating robust analytical methods and stringent quality control for co-formulated mAbs.[125] However, techniques such as size-exclusion chromatography, which is traditionally used to analyse degradation products of mAbs, cannot necessarily distinguish between two co-formulated mAbs and this poses analytical challenges which require novel solutions to ensure accurate and safe production.[127] Novel co-formulations would also likely necessitate new randomised control trials in order to obtain regulatory approval, even if the individual mAbs are already licenced for IBD and this adds further time and financial burden to development pipelines.

Despite these challenges, co-formulated mAbs are already in clinical use, particularly in oncology. One example is Phesgo, a fixed-dose combination of trastuzumab and pertuzumab used in the treatment of HER2-positive breast

Table 3 Glossary Table

Term	Definition
Fragment Crystallisable	The "tail" region of an antibody that interacts with cell surface receptors called Fc receptors and some proteins of the complement system.
Fragment Antigen-Binding Region	The region of an antibody responsible for binding to antigens.
Neonatal Fc Receptor	An IgG receptor that binds serum IgG and protects the IgG from degradation inside the lysosomes.
Single Chain Variable Fragments	A recombinant antibody fragment that retains the antigen-binding capacity of a full-length antibody but is smaller allowing better tissue penetration and easier manufacturing.
Linear Epitopes	A portion of an antigen that is recognised by antibodies and is made up of a continuous sequence of amino acids.
Conformational Epitopes	An antigen that is built from non-contiguous parts of the amino acid sequence through folding of the polypeptide chain in the native protein.
Aggregation	The self-association of individual mAbs to form larger oligomers
PEGylation	The process of attaching polyethylene glycol polymer chains to molecules and macrostructures, such as a monoclonal antibody
Glycosylation	A post-translational modification of proteins where glycans (sugars) are covalently attached to a macromolecule such as a monoclonal antibody.
Albumin Fusion	The attachment of a macromolecule to human albumin
Steric Hindrance	The slowing or prevention of a chemical reaction due to physical obstruction caused by the size and position of other atoms or groups within a molecule.
Antibody-drug conjugates (ADC)	Biopharmaceutical products in which a monoclonal antibody is linked to a small molecule drug with a stable linker.
Complementarity determining region (CDR)	The six hypervariable loops in an immunoglobulin molecule that form the three-dimensional cavity where an epitope binds to the antibody molecule.
Antibody-Dependent Cellular Cytotoxicity (ADCC)	A mechanism of cell-mediated immune defence whereby an effector cell of the immune system kills a target cell, whose membrane-surface antigens have been bound by specific antibodies.

cancer.[130] These two mAbs work synergistically to disrupt signalling pathways which would otherwise allow survival of neoplastic cells.[131] During its development, modifications were made to the formulation through the addition of vorhyaluronidase alfa and a histidine buffer to address concerns regarding the stability of the co-formulation which allowed subcutaneous administration.[130] Another example is Opdualag, which contains nivolumab and relatlimab-rmbw and is used for the treatment of unresectable or metastatic melanoma.[132] This formulation incorporates a histidine buffer, sucrose, and pentetic acid to ensure stability, safety, and efficacy.[124] These examples demonstrate that the challenges of co-formulation can be overcome through the use of computer modelling and bioengineering to ensure an effective and safe therapeutic agent. A glossary of terms used in this manuscript can be found in Table 3.

Conclusions

Monoclonal antibodies will remain a cornerstone of future IBD management. However, overcoming the therapeutic ceiling will require close collaboration among pharmaceutical scientists, bioengineers, industry partners, patients and clinicians. Harnessing cutting-edge technologies, including advanced protein engineering and machine learning, will be essential to designing novel therapies with enhanced precision and performance. Next-generation agents need to better target the cytokine networks driving IBD pathogenesis, while also demonstrating improved pharmacokinetic profiles and reduced immunogenicity. When paired with the rapidly advancing field of personalised IBD care, such therapies offer the potential to make substantial progress toward true disease clearance.[133]

Abbreviations

ABD, Albumin Binding Domains; ACT, Advanced Combination Therapy; ADA, Anti-drug Antibody; ADC, Antibody-Drug Conjugates; ADCC, Antibody-Dependent Cellular Cytotoxicity; bsAb, Bispecific Antibody; CDR, Complementarity Determining Region; CHO, Chinese Hamster Ovary Cells; Fab, Fragment antigen-binding; Fc, Fragment Crystallisable; FcRn, Neonatal Fc Receptor; IBD, Inflammatory bowel disease; IL – Interleukin; IMID, Immune Mediates Inflammatory Disorder; JAK, Janus Kinase; mAb, Monoclonal Antibody; NK, Natural Killer Cells; PEG, Polyethlyene Glycol; PK, Pharmacokinetic; scFvs, Single-chain variable fragments; SML, Sortase-mediated ligation; STAT, Signal transducer and activator of transcriptase proteins; TL1A, TNF-like ligand 1 A; TNF, Tumour Necrosis Factor.

Consent for Publication

All authors provide consent for publication of all materials contained within this review article including, but not limited to, images and tables.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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